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Signed Andrew Gerry

Dated 4 July 2003

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THE PATENT OFFICE
22 JUN 2002
NEWPORT

1/77

# Request for grant of a patent

*(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)*

22 JUN 2002

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — 00303 /GB

25JUN02 E728081-1 D10057
P01/7700 0.00-0214491.3

2. Patent application number *(The Patent Office will fill in this part)* — 0214491.3

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Norton Healthcare Limited
Ivax Quays
Albert Basin
Royal Docks
LONDON E16 2QT
GB

Patents ADP number *(if you know it)* 6188221004

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of invention — PHARMACEUTICAL COMPOSITION

5. Name of your agent *(if you have one)* — MARTIN ALEXANDER HAY

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

13 QUEEN VICTORIA STREET
MACCLESFIELD
CHESHIRE
SK11 6LP

Patents ADP number *(if you know it)* ~~4245677001~~ 8078438001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

| Country | Priority application number *(if you know it)* | Date of filing *(day / month / year)* |
|---|---|---|

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

| Number of earlier application | Date of filing *(day / month / year)* |
|---|---|

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

*a) any applicant named in part 3 is not an inventor, or*
*b) there is an inventor who is not named as an applicant, or*
*c) any named applicant is a corporate body*
*See note (d))*

No

**Patents Form 1/77**

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

| | |
|---|---|
| Continuation sheets of this form | 0 |
| Description | 7 |
| Claim(s) | 2 |
| Abstract | 1 |
| Drawing(s) | 0 |

CF

10. If you are also filing any of the following, state how many against each item.

| | |
|---|---|
| Priority documents | 0 |
| Translations of priority documents | 0 |
| Statement of inventorship and right to grant of a patent *(Patents Form 7/77)* | 0 |
| Request for preliminary examination and search *(Patents Form 9/77)* | 0 |
| Request for substantive examination *(Patents Form 10/77)* | 0 |
| Any other documents *(please specify)* | 0 |

11. I/We request the grant of a patent on the basis of this application

Signature Mark A Hay Date: 21 Jun 02

12. Name and daytime telephone number of person to contact in the United Kingdom

MARTIN A. HAY 01625 500057

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**Pharmaceutical Composition**

The present invention relates to a pharmaceutical composition. More particularly, it relates to an aerosol composition comprising a cannabinoid, to a metered dose inhaler containing the composition and to a method of administering the composition to a patient.

Cannabis is known to be useful in therapy, for example in the treatment nausea and vomiting associated with cancer chemotherapy, anorexia associated with AIDS, pain, epilepsy, glaucoma, asthma and mood disorders. The principle active ingredient in cannabis is delta-9-tetrahydrocannabinol (delta-9-THC). A derivative of delta-9-THC, which possesses similar properties, is delta-8-tetrahydrocannabinol (delta-8-THC). Collectively, cannabis, delta-9-THC and derivatives thereof, such as delta-8-THC, are known as cannabinoids.

International patent application publication number WO 01/66089 and United States patent application publication number 2002/0031480 disclose aerosol compositions comprising a cannabinoid and a propellant for administration to patients using a metered dose dispenser.

It is reported in WO 01/66089 that administration of aerosol compositions comprising the cannabinoid, delta-9-THC, and a propellant to the lungs of patients cause the patients to cough. Applicant has encountered a similar problem when administering aerosol formulations comprising delta-8-THC. This cough reaction is undesirable, because it results in exhalation of much of the inhaled dose.

Surprisingly, it has now been found that by incorporating a certain kind of ingredient into the aerosol compositions, the cough reaction of patients is suppressed.

According to one aspect, therefore, the present invention provides a pharmaceutical composition for administration as an aerosol, which comprises a cannabinoid, a propellant and an effective amount of a cough suppressant.

According to another aspect, the present invention provides the use of a cough suppressant in the manufacture of a pharmaceutical composition comprising a cannabinoid and a propellant to suppress coughing.

The cough suppressant may be, for example, a pharmaceutically acceptable aerosol surfactant; Suitable surface active agents include both non-fluorinated surfactants and fluorinated surfactants known in the art and disclosed, for example, in British Patent Nos. 837465 and 994734 and U.S. Patent No. 4,352,789. Examples of suitable surfactants include:

oils derived from natural sources, such as, corn oil, olive oil, cotton seed oil and sunflower seed oil; and

various groups of commercially available pharmaceutically acceptable surfactants sold under the trade names Span™, Tween™ and Brij™, and phospholipids, e.g. lecithin sold under the trade name Lipoid™.

Examples of particular commercially available pharmaceutically acceptable surfactants are:

Sorbitan trioleate available under the trade name Span 85;

Sorbitan monolaurate available under the trade name Span 20;

Polyoxyethylene (20) sorbitan monolaurate available under the trade name Tween 20;
Polyoxyethylene (20) sorbitan non-oleate available under the trade name Tween 80;

Lecithin derived from natural sources such as those available under the trade name Lipoid particularly Lipoid S100™;

Oleyl Polyoxyethylene (2) ether available under the trade name Brij 92;

Stearyl Polyoxyethylene (2) ether available under the trade name Brij 72;

Lauryl Polyoxyethylene (4) ether available under the trade name Brij 30;

Oleyl Polyoxyethylene (2) ether available under the trade name Genapol 0-020;

Block copolymers of oxyethylene and oxypropylene available under the trade name Synperonic, Oleic acid, Synthetic lecithin, Diethylene glycol dioleate, Tetrahydrofurfuryl oleate, Ethyl oleate, Isopropyl myristate, Glyceryl trioleate, Glyceryl monolaurate, Glyceryl mono-oleate, Glyceryl monostearate, Glyceryl monoricinoleate, Cetyl alcohol, Polyethylene glycol 400, Cetyl pyridinium chloride.

The cough suppressant may conveniently be present in a weight ratio of cough suppressant to cannabinoid of from 0.1:1 to 25:1.

When the cough suppressant is a pharmaceutically acceptable aerosol surfactant, the weight ratio of surfactant to cannabinoid in the composition is conveniently in the range of from 1:1 to 25:1, preferably 2:1 to 15:1, most preferably 3:1 to 10:1. This compares to the normal ratio of about 0.1:1 to 3:1 preferably 005:1 to 1:1 used in solution aerosols.

It will be appreciated by those skilled in the aerosol art that the use of a pharmaceutically acceptable aerosol surfactant as a cough suppressant is novel. According to another aspect therefore, the present invention provides the use of a pharmaceutically acceptable aerosol surfactant in the manufacture of pharmaceutical composition comprising a cannabinoid and a propellant for suppressing coughing.

In a second embodiment the cough suppressant may be an active substance used in the prevention or relief of asthma for example; a beta-agonist, such as salbutamol, formoterol,

salmeterol, pirbuterol, terbutyline; or a steroid, such as beclamethasone, budesonide or fluticasone.

In a third embodiment, the cough suppressant may be an anti-tussive agent e.g. Guiaphenesin, Dextromethorphan etc.

When the cough suppressant is a beta agonist or steroid, the weight ratio of beta agonist or steroid to cannabinoid in the composition is conveniently in the range of from 0.1:1 to 5:1.

The cannabinoid may be, for example, an extract of natural cannabis, delta-9-THC, a derivative of delta-9-THC such as delta-8-THC, or a mixture of any of these.

The propellant may be, for example, an alkane, such as butane, or a fluorocarbon, such as 1,1,1,2-tetrafluoroethane (P-134a) or 1,1,1,2,3,3,3-heptafluoropropane (P-227). Preferably it is P-134a.

The weight ratio of propellant to cannabinoid in the composition is conveniently in the range of from 250:1 to 10,000:1.

The composition may further comprise one or more carriers or excipients, such as a pharmaceutically acceptable solvent, for example an alcohol, such as ethanol, isopropanol or glycerol. Solid bulking agents such as a sugar e.g. Lactose, Trehalose etc. may be used or IPA Glycerol, lactose. A further preferred option is the use of coated particles of the active substance. The coating may consist of a sugar, or a pharmaceutically acceptable polymer e.g. polyvinyl pyrrolidone, hydroxyproplymethyl cellulose, hydroxypropyl cellulose etc. The coating may also be a surfactant, most preferably one from the previous list which is solid at room temperature. The coating must of course be preferably water-soluble so that the active molecule is quickly released in vivo. The coated particles may be made by any suitable technique, most preferably by spray drying. Preferably, any carrier or excipient present in the composition is selected

from ethanol. The ethanol should be between 0.1% to 25% of the formulation, most preferably 1% to 25% of the formulation, most preferably 1% to 15%. The formulation may in addition include any excipient or drug previously mentioned. The drug if used can either be in suspension or if soluble in a P134a / Ethanol mixture, in solution.

The one or more carriers or excipients may conveniently comprise from 0 to 25 % by weight of the total composition.

The pharmaceutical composition according to the invention may conveniently be administered to a patient using a metered dose device, such as a metered dose inhaler. According to another aspect, therefore, the present invention provides a metered dose device containing a pharmaceutical composition according to the invention.

According to another aspect, the present invention provides a method of administering an aerosol comprising a cannabinoid and a propellant to a patient, which comprises administering the cannabinoid and propellant with an effective amount of a cough suppressant.

The cough suppressant may be administered to the patient in a pharmaceutical composition comprising the cannabinoid and propellant or separately. If it is administered separately, it should be administered at the same time or before the cannabinoid and propellant. For example, if the cough suppressant is a beta agonist, the patient may first inhale a dose of beta agonist, then an aerosol comprising the cannabinoid and propellant. Preferably, the method comprises administering a pharmaceutical composition comprising a cannabinoid, a propellant and a cough suppressant as described herein above.

As used herein, the term patient refers to any human or non-human animal. Preferably the patient is a human.

The aerosol may be administered via a pulmonary, sub-lingual, nasal or buccal route.

The following Examples illustrate the invention.

**Example 1**

| Ingredient | Weight in g |
|---|---|
| Ethanol | 0.10 |
| P-134a | 2.02 |
| delta-8-THC | 0.01 |
| Lipoid S100 | 0.05 |

**Example 2**

| Ingredient | Weight in g |
|---|---|
| Ethanol | 0.09 |
| P-134a | 1.83 |
| delta-8-THC | 0.01 |
| Brij™ | 0.02 |

**Example 3**

| Ingredient | Weight in g |
|---|---|
| Ethanol | 0.20 |
| P-134a | 3.80 |
| delta-8-THC | 0.01 |
| Salbutamol Sulphate | 0.01 |

**Comparative Example 1 - Oil forms slowly on standing after P134a addition.**

| Ingredient | Weight in g |
|---|---|
| Ethanol | 0.20 |
| P-134a | 4.40 |
| delta-8-THC | 0.02 |
| Glycerol | 0.04 |

**Comparative Example 2**

| Ingredient | Weight in g |
|---|---|
| Ethanol | 0.10 |
| P-134a | 2.48 |
| delta-8-THC | 0.01 |
| Isopropylmyristate | 0.06 |

The effect of administering the compositions of the Examples and Comparison Examples on patients was investigated as follows:-

The examples were filled in Standard glass vials with a normal valve and seals. The completed units were put in a standard actuator and primed. Then one puff of each was taken in the normal manner by the volunteer.

The results were as described in Table 1 below:-

**Table 1**

**Evaluation of Test Compositions for Cough**

| **Composition** | **Effect** |
|---|---|
| Comparative Example 1 | Spontaneous cough within 2-3 sec |
| Comparative Example 2 | Spontaneous cough within 2-3 sec |
| Example 1 | No cough, no burning sensation |
| Example 2 | No cough, burning sensation in lungs |
| Example 3 | Weak cough, no burning sensation |

Claims

1. A pharmaceutical composition for administration as an aerosol, which comprises a cannabinoid, a propellant and an effective amount of a cough suppressant.

2. A composition as claimed in Claim 1, in which the cough suppressant is a pharmaceutically acceptable aerosol surfactant; a beta-agonist or a steroid; or an anti-tussive agent.

3. A composition as claimed in Claim 2, in which the cough suppressant is a pharmaceutically acceptable aerosol surfactant selected from oils derived from natural sources; and commercially available pharmaceutically acceptable surfactants sold under the trade names Span™, Tween™ and Brij™, and phospholipids.

4. A composition as claimed in Claim 3, in which the cough suppressant is Lipoid S100™.

5. A composition as claimed in Claim 2, in which the cough suppressant is a beta-agonist or a steroid selected from salbutamol, formoterol, salmeterol, pirbuterol, terbutyline, beclamethasone, budesonide and fluticasone

6. A composition as claimed in Claim 2, in which the cough suppressant is an anti-tussive agent selected from Guiaphenesin and Dextromethorphan

7. A composition as claimed in any one of Claims 1 to 6, in which the propellant is 1,1,1,2-tetrafluoroethane.

8. A composition as claimed in any one of Claims 1 to 7, which further comprises ethanol.

9. A metered dose dispenser, which contains a pharmaceutical composition as claimed in any one of Claims 1 to 8.

10. The use of a cough suppressant in the manufacture of a pharmaceutical composition comprising a cannabinoid and a propellant to suppress coughing.

11. The use of a pharmaceutically acceptable aerosol surfactant in the manufacture of a pharmaceutical composition comprising a cannabinoid and a propellant to suppress coughing.

12. A method of administering an aerosol comprising a cannabinoid and a propellant to a patient, which comprises administering the cannabinoid and propellant with an effective amount of a cough suppressant.

# Abstract

A pharmaceutical composition for administration as an aerosol, which comprises a cannabinoid, a propellant and an effective amount of a cough suppressant.